**REPLY PURSUANT TO 37 C.F.R. § 1.111**

## REMARKS

Claims 1-30 are currently pending in the application and claims 1-30 stand rejected. The Examiner in his Office Action noted that the drawing filed on June 26, 2003, is accepted, a claim for foreign priority under 35 USC § 119(a)-(d) or (f) is acknowledged and the certified copy of the priority document(s) is acknowledged as received. By way of this amendment claims 1, 2 and 30 have been amended to recite more distinctly the invention of this application, and to overcome the outstanding rejections as discussed in detail below, and claims 11 and 12 are cancelled without prejudice. All amendments to the claims have been made in accordance with the procedures set out in 37 C.F.R. § 1.121(c). No new subject matter has been added through these amendments. Applicants respectfully traverse the outstanding rejections as set forth below.

## REJECTIONS

**Rejection under 35 U.S.C. §112, second paragraph:**

Claims 1-28 and 30 are rejected under 35 U.S.C. §112, second paragraph, allegedly because the specification, while being enabling for treating a disease amenable to treatment with a compound that both inhibits angiotensin converting enzyme and neutral endopeptidase, does not reasonably provide enablement for the treatment of "a disease" in general. The Examiner alleges that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims." The Examiner further alleges that "the present objective of treating 'a disease' reads on a panacea, i.e., treating a patient for any and all purposes, and the art currently is unaware of any single agent, or combination of agents that could be used for the treatment of any and all disease states." The Examiner suggests that this rejection may be overcome by amending claim 1 to read, in part, "--A method of inhibiting both angiotensin converting enzyme and neutral endopeptidase for the treatment of a disease amenable to treatment with an a compound that both inhibits angiotensin converting enzyme and neutral endopeptidase which comprises...--" The Examiner also suggested similar amendment to claim 30.

Applicants carefully considered the Examiner's comments and recommendations. Applicants amended claim 1 to insert --amenable to treatment with a compound that inhibits both angiotensin converting enzyme and neutral endopeptidase-- before the word "which" in said claim. Claim 30 was amended to delete "comprising" and insert in its place --amenable to treatment with a compound that inhibits both angiotensin converting enzyme and neutral endopeptidase which comprises--.

In view of the foregoing, Applicants submit that this rejection as to claims 1-28 and 30 is rendered moot. Therefore, Applicants respectfully request withdrawal of this rejection of claims 1-28 and 30.

**Rejection under 35 U.S.C. § 102(b) or rejection under 35 U.S.C. § 103(a)**

Claims 1-3 and 11-30 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Flynn et al. (U.S. Patent No. 5,430,145, cited by Applicants) who teach methods for treating renal diseases, i.e., nephropathies, arteriosclerosis and vascular myointimal thickening following balloon injury, i.e., vascular endothelial dysfunction, (col. 2, lines 13, 44 and 49) which comprises the administration of the presently claimed compounds (col. 3, line 1- col. 4, line 68 as well as the Certificate of Correction Sheets) as well as method for the preparation of pharmaceutical compositions which comprise the presently claimed compounds by mixing such compounds with one or more pharmaceutically acceptable excipients (col. 70, line 14 – col.71, line 17). The Examiner alleges that "Should the compounds not be anticipated, they would have nevertheless been obvious from the teaching at col. 3, line 1 – col. 4, line 68 as well as the Certificate of Correction sheets where the basic structure of the present compounds as well as the moieties necessary to form the specifically claimed compounds are provided for." The Examiner further alleges that "While Flynn et al. are silent as to the activity of the compounds as neutral peptidase inhibitors, such would be inherent in the prior art because the same compounds are being administered to the same patients for the same therapeutic purposes."

With respect to the alternative rejection under 35 U.S.C. 102(b) or 35 U.S.C. 103(a), applicants do not consider the claimed subject matter to read exactly on the prior art and thus applicants do not consider the rejection under 35 U.S.C. 102(b) as proper. Applicants have thus responded to the rejection under 35 U.S.C. 103(a).

Claims 1-3 and 11-30 were rejected under 35 USC 103(a) as being unpatentable independently over Flynn et al. (U.S. Patent No. 5,430,145, hereinafter '145). U.S. Patent No. '145 discloses mercaptoacetylamide derivatives that are useful as inhibitors of NEP (enkephalinase) and ACE. Applicants acknowledged on page 2 of the specification that the instant invention relates to specific compounds within the claimed generic disclosure of the '145 patent and, as stated in the instant Summary of Invention, this application is directed to the use of said compounds of formula (I), and the various embodiments thereof, for the treatment and/or prophylaxis of nephropathy in diabetic or non-diabetic patients, including diabetic and non-diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndome, hypertensive nephrosclerosis, microalbuminuria or end stage renal disease, or to a method of treatment and/or prophylaxis of insulin resistance or of metabolic diseases associated with advanced glycation end-products, diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, myocardial infarction and/or diabetic cardiomyopathy, or to a method of treatment and/or prophylaxis of atherosclerosis or endothelial dysfunction.

Accordingly, applicants respectfully traverse this rejection based on the following arguments. First, as noted above, applicants reiterate that the court(s) have declined to extract from *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989) the rule "that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it," and "every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." *In re Jones*, 958 F.2d at 350-51, 21 USPQ.2d at 1943 (Fed. Cir. 1992).

Secondly, (as outlined in MPEP 2144.08, II) to establish a proper prima facie case of unpatentability the Examiner should consider the factors set out by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Thus to make a case of obviousness Examiner must:

1. determine the scope and contents of the prior art;

2. ascertain the differences between the prior art and the claims in issue;
3. determine the level of ordinary skill in the pertinent art [at the time the invention was created], and
4. evaluate any evidence of secondary considerations.

If evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a prima facie case of obviousness (MPEP 2144.08, II, A). In addition, as required under point 4 of this analysis, applicants respectfully bring to the attention of the Examiner that no mention of evaluation of secondary considerations was made in the office action. Applicants respectfully submit that evidence of a superior nephroprotective effect is stated on page 13 of the specification, lines 15-20, and is supported by experimental data for examples 1-3 with respect to urinary albumin excretion data. The data supporting a superior nephroprotective effect further supports utility of these compounds for the treatment and or prevention of nephropathy in diabetic and non-diabetic patients including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephritic syndrome, hypertensive nephrosclerosis, microalbuminuria and end stage renal disease as indicated on page 13, lines 15-20, of the specification.

A prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967). When an applicant demonstrates substantially improved results and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary. *In re Soni*, 54 F.3d 746, 34 USPQ 2d 1688 (Fed. Cir. 1995)

Based on the foregoing, applicants respectfully submit that claims 3 and 4 are supported by evidence of a superior nephroprotective effect and that the rejection to claim 3 be withdrawn. Additionally, after reviewing the Examiner's comments and rejections, Applicants respectfully cancel claims 11 and 12. Claim 2 was amended to delete recitation of the diseases atherosclerosis and endothelial dysfunction that were each individually claimed in dependent claims 11 and 12, respectively.

Based on the foregoing, Applicants respectfully request withdrawal of this rejection to claims 1-3 and 13-30.

**Comments regarding claims 4 and 6-9**

With respect to claims 4 and 6-9, the Examiner comments that "Claims 4 and 6-9 are directed to certain disease[s] that the Examiner believes would have been obvious in view of Moskowitz (U.S. Patent Application Publication 2003/0040509)". The Examiner's basis for this belief is "because Moskowitz teaches that angiotensin converting enzyme inhibitors could be used to treat diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, myocardial infarction and cataracts (page 2, Table 1 and page 14, col. 2, claim 16), while the presently claimed compounds were known from Flynn et al (above) to possess, in part, angiotensin converting enzyme inhibitory activity. The Examiner alleges that "The present claims, however, would not be properly rejected because claim 1 (and claim 29) is directed to the inhibition of both angiotensin converting enzyme and neutral endopeptidase in a patient in need thereof. Furthermore the Examiner alleges that "The objective of inhibiting neutral endopeptidase is not taught by either Moskowitz or Flynn et al., and one cannot conclude that such an objective would be inherent when considering the subject matter of claims 4 and 6-9. The examiner indicates the preceding is "so because for inherence, as set forth in MPEP 2112:

'To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherence, however, may not be established by probabilities or possibilities. The mere fact that a certain thin may result from a given set of circumstances is not sufficient.' "In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)".

The Examiner summarizes the foregoing by indicating, "That is, by saying that it would have been obvious to treat the conditions of claims 4 and 6-9 with the claimed compounds by taking the teachings of Flynn et al. in view of Moskowitz, it would be equivalent to saying that it would have been probable or possible for the skilled artisan to have used the presently claimed compounds for the treatment of the diseases of claims 4 and 6-9. Thus, "Such a condition of probability or possibility dictates against a finding of inherency and "Accordingly, claims 4 and 6-9 are not subject to the above rejection."

Although claims 4 and 6-9 are not subject to the above rejection, applicants wish to point out that the Moskowitz reference would be inappropriate to combine with Flynn et al. '145. Moskowitz teaches that it is necessary to administer an amount of an ACE inhibitor effective to inhibit tissue ACE by greater than 95% as the target dose for maximally effective disease prevention. As such, Moskowitz teaches away from combined inhibition of enkephalinase and ACE taught by Flynn et al '145. This "teaching away" is even more apparent based on applicants' discovery of a superior nephroprotective effect associated with combined inhibition of ACE and NEP versus ACE inhibition alone as discussed above.

Based on the foregoing amendments to claims 1, 2 and 30, cancellation of claims 11 and 12, and the Examiner's statement that claims 4 and 6-9 are not subject to the above rejection, Applicants respectfully request allowance of claims 4 and 6-9.

**Comments Regarding Claims 5 and 10**

With respect to claims 5 and 10, the Examiner comments that "Claims 5 and 10 are free of the prior art issue because the prior art fails to teach the treatment of insulin resistance or diabetic cardiomyopathy with the presently claimed compounds. However, the Examiner then stated "None of the claims are allowed."

Based on the foregoing amendments to claims 1, 2 and 30, cancellation of claims 11 and 12, and the Examiner's statement that claims 5 and 10 are free of the prior art, Applicants respectfully submit that claims 1-10, 13-30 as amended, are in condition for an immediate allowance and such an action is earnestly requested.

**CONCLUSION**

Applicants respectfully submit that the claims 1-10 and 13-30 are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions please call (collect if necessary) the undersigned agent at the telephone number listed below.

The Commissioner is hereby authorized to charge these fees and any other fees that are due to this paper to Deposit Account No. **18-1982** for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,

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